THE ADDITION OF HETEROCYCLIC AMINES TO CINNAMATE ESTERS

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The author thanks Dr. A. H. Gropp for his many suggestions and advice on certain phases of this work.

For her support and encouragement the author wishes to express his gratitude to his wife, Jean.

PREFACE

The experimental work described in this dissertation is purposely presented in detailed form to facilitate duplication by future investigators. Every synthesis is reported in detail, even though the basic procedure in a given series is essentially the same.

Throughout this dissertation all melting points reported are corrected values. The thermometers used were calibrated against a set of thermometers standardized by the Bureau of Standards. In conformity with present practice, all temperatures reported refer to the Centigrade scale; the symbol is omitted.

The manner of listing references is the customary one for technical reports. Journal abbreviations are those used by Chemical Abstracts.

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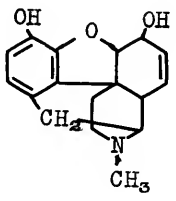
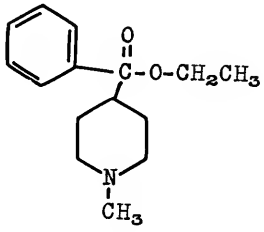
CHAPTER I

INTRODUCTION

For many years a search has been under way for a synthetic drug which possesses an analgesic potency similar to that of morphine (I) but lacks the undesirable side effects and addiction liabilities of this alkaloid. One of the milestones in this search was the synthesis of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate (II) in 1937 by Eisleb and Schaumann.[1]



I



II

Under the name Demerol[(a)] this drug has found wide clinical use in recent years. Although a less potent analgetic than morphine, Demerol is less toxic and causes less euphoria and sedation.[2] It has been found to cause definite

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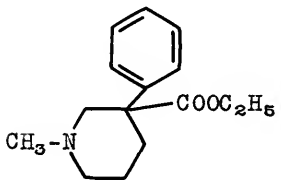
(a) Other names: Meperidine, Pethidine, Dolantin, Isonipecaine

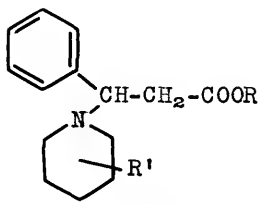
true addiction, but the withdrawal symptoms are milder than those caused by morphine.[3]

In 1944 an analog of Demerol in which the 3- instead of the 4-position of the piperidine is substituted was synthesized by Bergel *et al.*[4] It has been reported that this compound (III), ethyl 1-methyl-3-phenylpiperidine-3-carboxylate, retains the analgetic action of Demerol, but causes less sedation.[5] This would indicate that substitution in the 4-position is not essential to analgetic activity in piperidine derivatives.

The object of the present research was to synthesize ester derivatives of piperidine of the general form IV in the hope of obtaining a clinically useful analgesic.

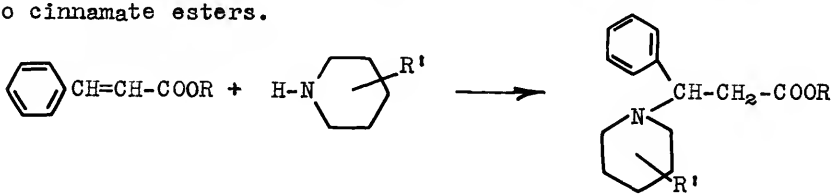


III



IV

It was decided to attempt the formation of these compounds by the addition of heterocyclic secondary amines to cinnamate esters.



The addition of amines to acrylate esters constitutes a useful method of synthesizing N-substituted beta-amino propionate esters. However, there are few literature reports of the reaction of amines with the less reactive substituted acrylate esters such as the cinnamate esters. There is no reference in the literature to a successful addition of a secondary amine to a cinnamate ester.

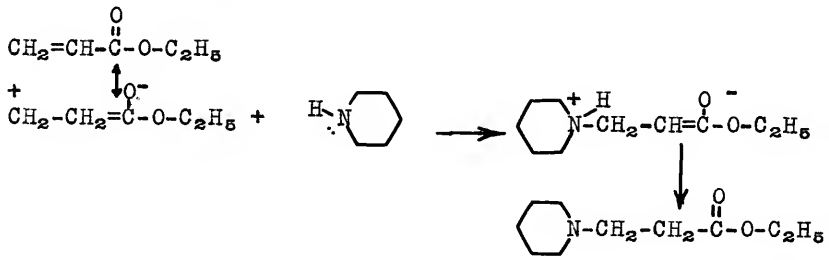
CHAPTER II

DISCUSSION OF THE REACTION

The Addition of Amines to Olefinic Esters

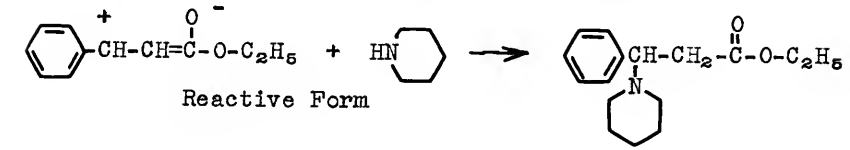
Amines do not generally react with olefins under ordinary conditions. However, in many cases they add readily to conjugated olefins such as acrylonitrile,[6] beta-keto olefins,[7] and the acrylate esters[8] to form the beta-amino compounds.

The mechanism of this addition reaction is thought to be a nucleophilic attack by the amine or amine anion upon a carbonium ion.[9] Considering the reaction of piperidine with ethyl acrylate, this mechanism can be illustrated in the following manner:

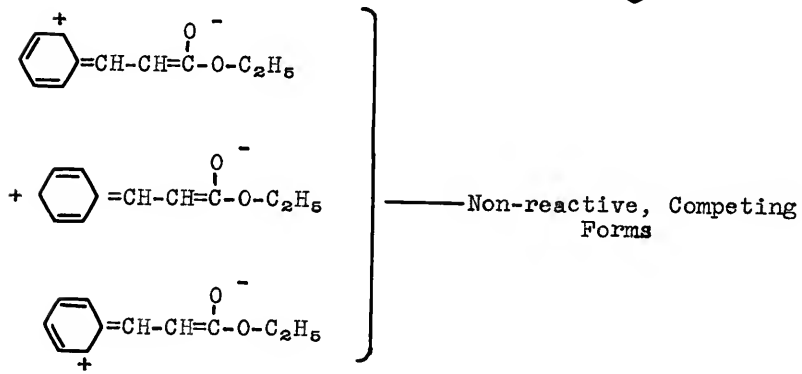


It is probable that a secondary amine reacts with a cinnamate ester according to a similar scheme. However, in this case there are three additional, nonreactive resonance

forms which could tend to make the olefin less reactive by decreasing the positive charge on the beta-carbon atom.



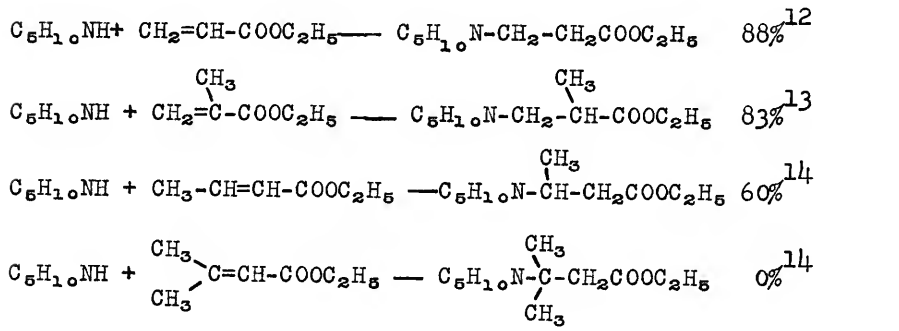
Reactive Form



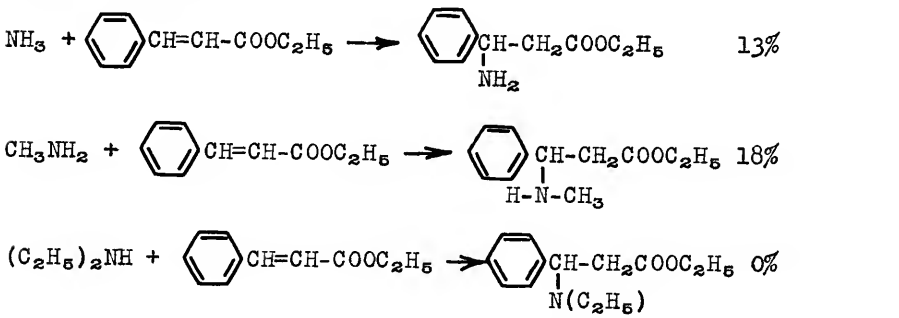
Non-reactive, Competing Forms

The Michael reaction, in which the anion of an active hydrogen compound adds to the beta-carbon atom of an unsaturated ester, is believed to proceed by the same type of mechanism.[9] C. K. Ingold, in his discussion on the effect of structure on equilibrium in this reversible reaction, states that beta-aryl groups are thermodynamically inhibitory towards addition due to conjugation with the double bond.[10] In addition, steric effects may also tend to decrease the reactivity of the beta-substituted olefinic esters.[11]

This decreased reactivity of substituted acrylic esters can be illustrated by considering the yields of beta-amino esters obtained by the reaction of piperidine with various esters:



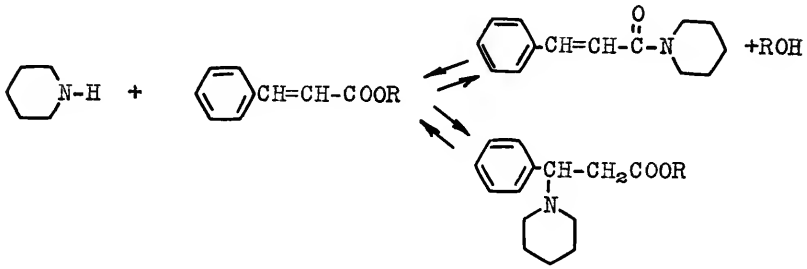
The products of the reactions of ammonia and amines with ethyl cinnamate have been studied by Karl Morsch.[15] The yields of beta-amino ester isolated from the reaction mixtures are listed below:



The only product obtained from the reaction of diethylamine with ethyl cinnamate was the amide, N,N-Diethylcinnamide, in 39.9% yield.

Evidence of the reversibility of the reaction of amines with unsaturated esters is provided by the work of McElvain and Stork.[16]

In addition to the reaction of the amine with the olefinic bond, it is also possible for ammonolysis of the ester group to occur. This competing reaction is known to take place, and under certain conditions the amide is the only product isolated.



CHAPTER III

EXPERIMENTAL

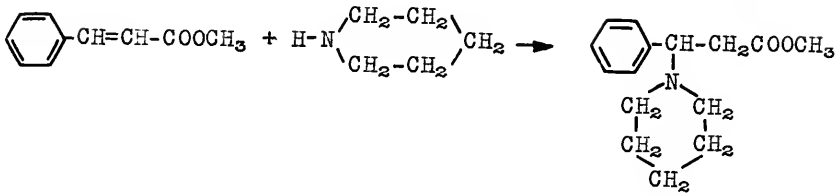
Part 1: The Preparation of 2-(N-Heterocyclic)-2-phenyl-propionate Esters

The reaction of heterocyclic amines with cinnamate esters was effected by refluxing equimolar quantities of the reactants with or without a solvent. The method used to isolate the product was basically the same in all cases. The reaction mixture was first washed with distilled water to remove unchanged amine. The solution was then extracted with a dilute acid solution to remove the product from the reaction mixture. This acid solution was then made basic, causing the product to separate out as an oil. This oil was taken up in ether and the ether solution was dried. The product was isolated from the ethereal solutions by precipitation as the hydrochloride salt. This method of working up the products was employed because it was found that vacuum distillation of the reaction mixture led to formation of the corresponding amide.

The percentage yields of products are based upon the molar quantity of cinnamate ester used. Unless otherwise noted, they refer to purified product.

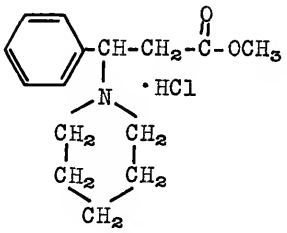
All of the products were analyzed for carbon and hydrogen content. These microanalyses were done by Geller Laboratories.

Methyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Sixteen and two-tenths grams of methyl cinnamate and 8.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was then treated with dry hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2. Yield: 4.6 g., or 18.6%.

Methyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . $C_{16}H_{22}N\ O_2Cl$

Molecular Weight. 283.80

Melting Point. . . . . .190.5 - 191.5

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 63.47

Found 63.34

Hydrogen, %

Calculated. 7.82

Found 7.95

Solubilities:

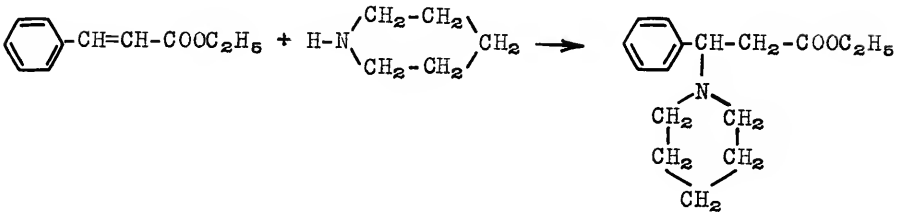
Water. . . . . .Very Soluble

Ethanol. . . . . Soluble

Acetone. . . . . Insoluble

Benzene. . . . . Insoluble

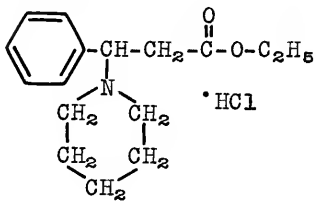
Ethyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Seventeen and six-tenths grams of ethyl cinnamate and 8.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was then treated with dry hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2.

Yield: 6.0 g., or 20.1%.

Ethyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{16}H_{24}N\ O_2Cl$

Molecular Weight. 297.82

Melting Point. . . . . 195 - 195.5

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 64.52

Found. 64.36

Hydrogen, %

Calculated. 8.12

Found. 8.22

Solubilities:

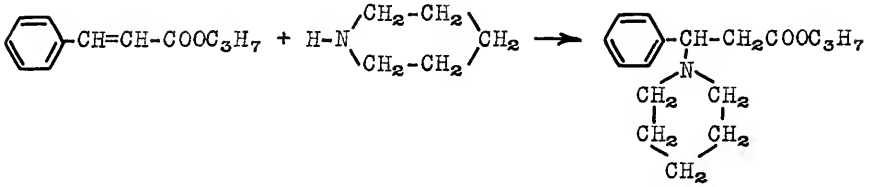
Water. . . . . .Very Soluble

Ethanol. . . . . Soluble

Acetone. . . . . Insoluble

Benzene. . . . . Insoluble

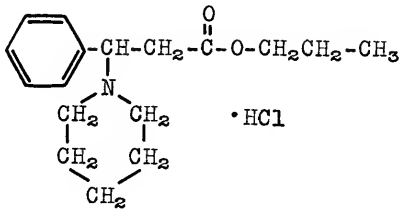
n-Propyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Nineteen grams of n-propyl cinnamate and 8.5 g. of piperidine were dissolved in 30 ml. of heptane and the solution was refluxed for eight hours. After the solution had cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was then recrystallized from propanol-2.

Yield: 7.0 g., or 22.4%.

n-Propyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{17}H_{26}N\ O_2Cl$

Molecular Weight. 311.85

Melting Point. 200.5

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 65.47

Found. 65.83

Hydrogen, %

Calculated. 8.42

Found. 8.55

Solubilities:

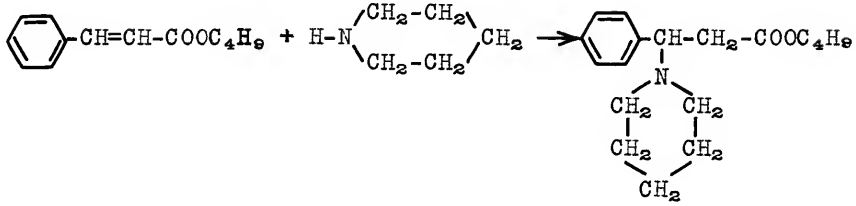
Water. . . . . Very Soluble

Ethanol. . . . . .Soluble

Acetone. . . . . .Insoluble

Ether. . . . . .Insoluble

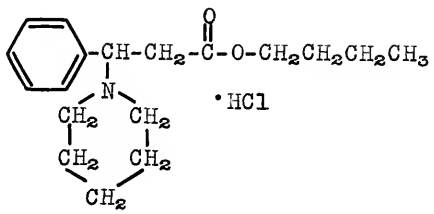
n-Butyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Thirty-five and six-tenths grams of n-butyl cinnamate and 15.0 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 8.9 g., or 15.6%.

n-Butyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{18}H_{28}N\ O_2Cl$

Molecular Weight. 325.87

Melting Point. . . . . 169 - 170

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 66.33

Found. 66.44

Hydrogen, %

Calculated. 8.67

Found. 8.85

Solubilities:

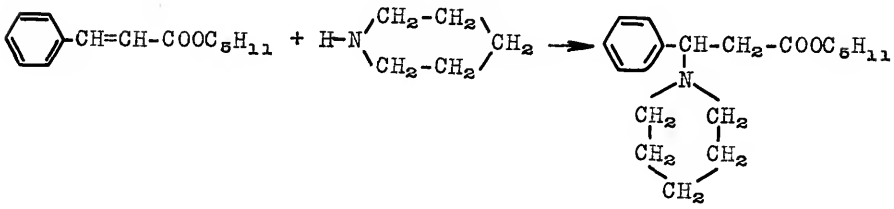
Water. . . . . .Very Soluble

Ethanol. . . . . Soluble

Acetone. . .Slightly Soluble

Ether. . . . . Insoluble

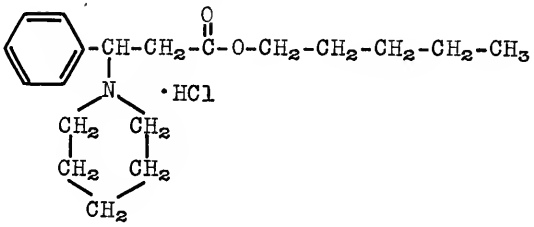
n-Amyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Thirty-seven grams of n-amyl cinnamate and 16.0 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized from a mixture of propanol-2 and acetone.

Yield: 7.3 g., or 12.2%.

n-Amyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . $C_{19}H_{30}NO_2Cl$

Molecular Weight 339.90

Melting Point. . . . . 171.5 - 172.5

Recrystallizing Solvent. . . . . Propanol-2, Acetone

Analyses:

Carbon, %

Calculated. 67.13

Found. 67.24

Hydrogen, %

Calculated. 8.91

Found. 8.76

Solubilities:

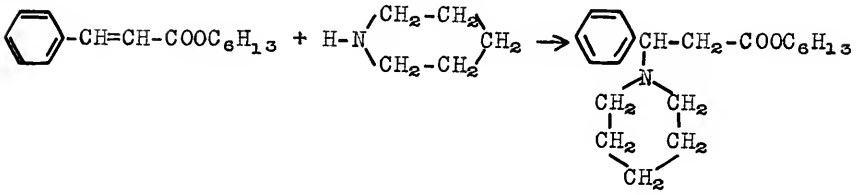
Water. . . . . .Very Soluble

Ethanol. . . . . Soluble

Acetone. . . . . .Slightly Soluble

Ether. . . . . Insoluble

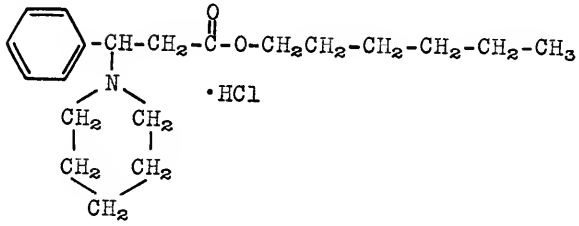
n-Hexyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Twenty-three and one-tenth grams of n-hexyl cinnamate and 8.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty-four hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized from benzene.

Yield: 2.8 g., or 7.9%.

n-Hexyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{20}H_{32}N\ O_2Cl$

Molecular Weight. 353.93

Melting Point. . . . . 131 - 132

Recrystallizing Solvent. . . . . Benzene

Analyses:

Carbon, %

Calculated. 67.86

Found. 67.76

Hydrogen, %

Calculated. 9.13

Found. 9.22

Solubilities:

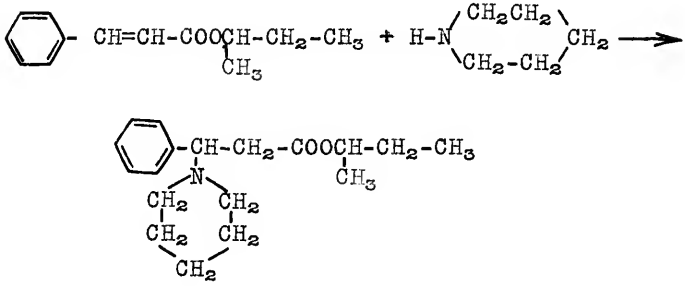
Water. . . . . Soluble

Ethanol. . . . . Soluble

Acetone. . . . . .Slightly Soluble

Ether. . . . . Insoluble

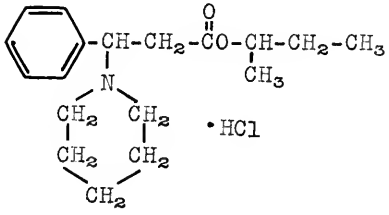
1-Methylpropyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Thirty grams of 1-methylpropyl cinnamate and 12.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 3.0 g. or 6.3%.

1-Methylpropyl 2-(1-Piperidyl)-2-phenyl-propionate
Hydrochloride



Molecular Formula. . . . . $C_{18}H_{28}N\ O_2Cl$

Molecular Weight. 325.87

Melting Point. . . . . .189.5 - 190

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 66.33

Found. 66.48

Hydrogen, %

Calculated. 8.67

Found. 8.57

Solubilities:

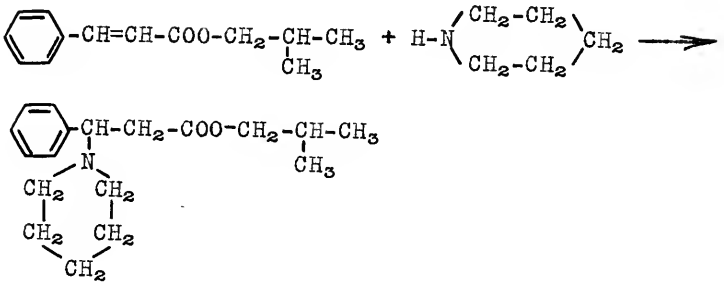
Water. . . . . .Soluble

Ethanol . . . . . Soluble

Acetone. .Very Slightly Soluble

Ether. . . . . .Insoluble

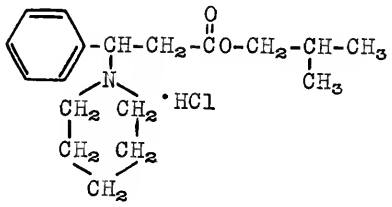
2-Methylpropyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Thirty grams of 2-methylpropyl cinnamate and 12.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 3.1 g., or 6.5%.

2-Methylpropyl 2-(1-Piperidyl)-2-phenyl-propionate
Hydrochloride



Molecular Formula. . . . . $C_{18}H_{28}N\ O_2Cl$

Molecular Weight. 325.87

Melting Point. . . . . 160 - 161

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 66.33

Found. 66.16

Hydrogen, %

Calculated. 8.67

Found. 8.55

Solubilities:

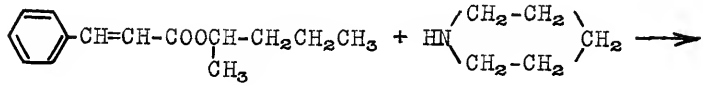
Water. . . . . .Soluble

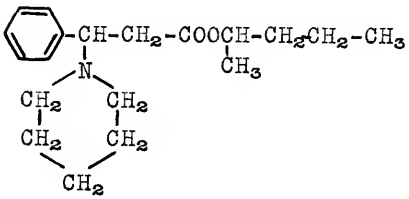
Ethanol. . . . . .Soluble

Acetone. . . . Slightly Soluble

Ether. . . . . .Insoluble

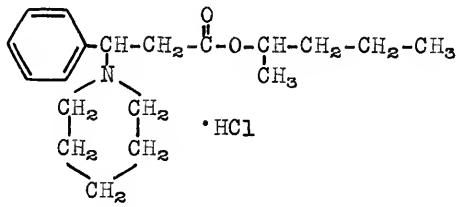
1-Methylbutyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride





Thirty-five grams of 1-methylbutyl cinnamate and 14 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2. Yield: 2.0 g., or 3.7%.

1-Methylbutyl 2-(1-Piperidyl)-2-phenyl-propionate
Hydrochloride



Molecular Formula. . . . . $C_{18}H_{30}N\,O_2Cl$

Molecular Weight. 339.90

Melting Point. . . . . .167 - 168

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 67.13

Found 67.10

Hydrogen, %

Calculated 8.91

Found 8.87

Solubilities:

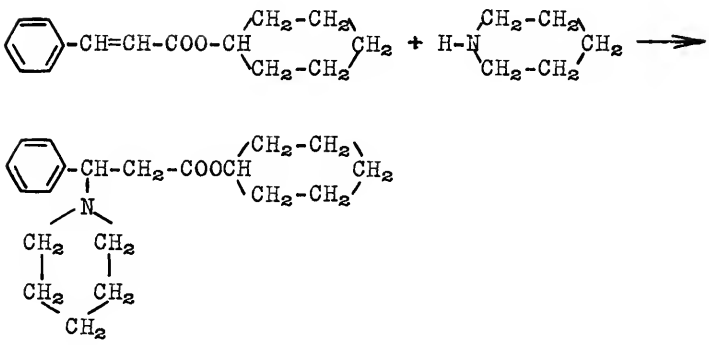
Water. . . . . Soluble

Ethanol . . . . . .Soluble

Acetone. . . .Slightly Soluble

Ether. . . . . Insoluble

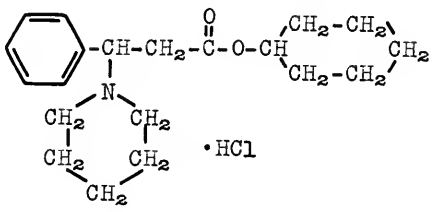
Cyclohexyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Forty grams of cyclohexyl cinnamate and 15.0 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 6.0 g., or 9.9%.

Cyclohexyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{20}H_{30}N\ O_2Cl$

Molecular Weight. 351.91

Melting Point. . . . . 182.3 - 182.5

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 68.26

Found. 68.00

Hydrogen, %

Calculated. 8.59

Found. 8.45

Solubilities:

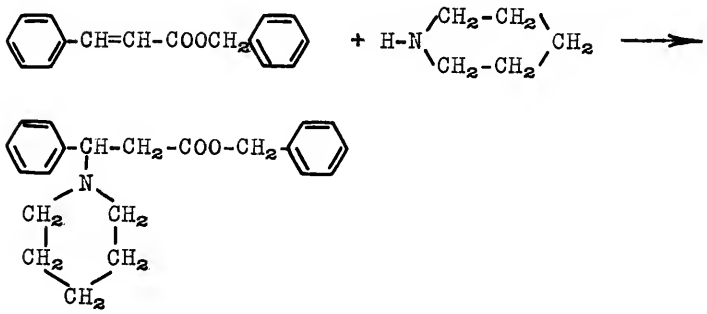
Water. . . . . .Soluble

Ethanol . . . . . Soluble

Acetone. . . . Slightly Soluble

Ether. . . . . .Insoluble

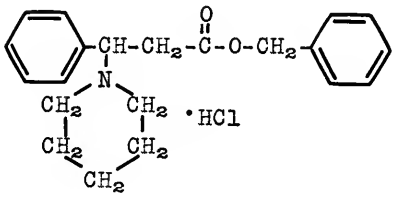
Benzyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Twenty-three and eight-tenths grams of benzyl cinnamate and 8.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was then treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2.

Yield: 7.3 g., or 20.3%.

Benzyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . $C_{21}H_{26}N\ O_2Cl$

Molecular Weight. 359.88

Melting Point. . . . . 191.5 - 192

Recrystallizing Solvent Propanol-2

Analyses:

Carbon, %

Calculated. 70.08

Found. 69.72

Hydrogen, %

Calculated. 7.28

Found. 7.32

Solubilities:

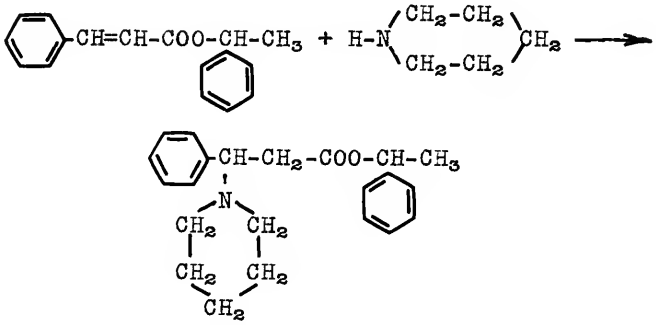
Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Acetone. . . . . Slightly Soluble

Ether. . . . . .Insoluble

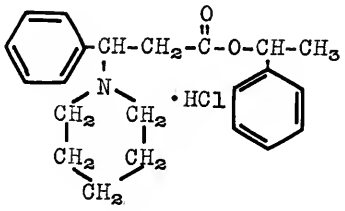
1-Phenylethyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Thirty-three grams of 1-phenylethyl cinnamate and 11.2 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2.

Yield: 6.8 g., or 13.5%.

1-Phenylethyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{22}H_{28}N\ O_2Cl$

Molecular Weight. 385.92

Melting Point. . . . . 182.3 - 182.8

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 70.66

Found. 70.65

Hydrogen, %

Calculated. 7.55

Found. 7.65

Solubilities:

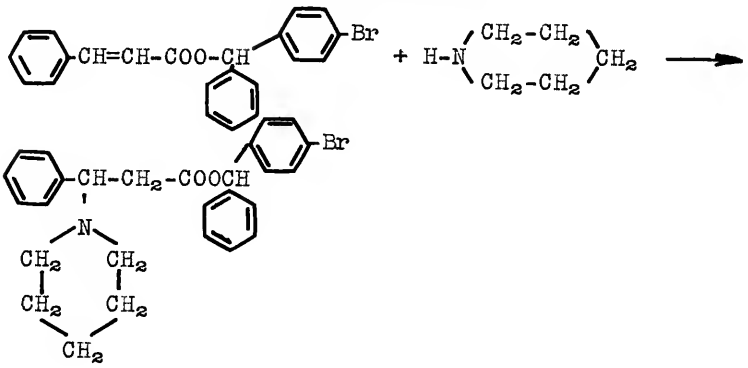
Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Acetone. . . . . .Insoluble

Ether. . . . . .Insoluble

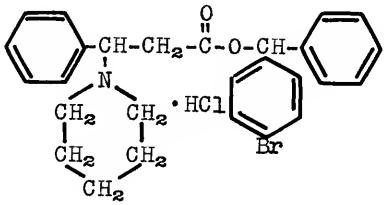
p-Bromobenzhydryl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Fifteen grams of p-bromobenzhydryl cinnamate and 5.0 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 4.8 g., or 24.4%.

p-Bromobenzhydryl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . $C_{27}H_{28}NO_2ClBr$

Molecular Weight 514.89

Melting Point. . . . . 179.5 - 180.5

Analyses:

Carbon, %

Calculated. 62.97

Found 62.53

Hydrogen, %

Calculated. 5.68

Found 5.67

Solubilities:

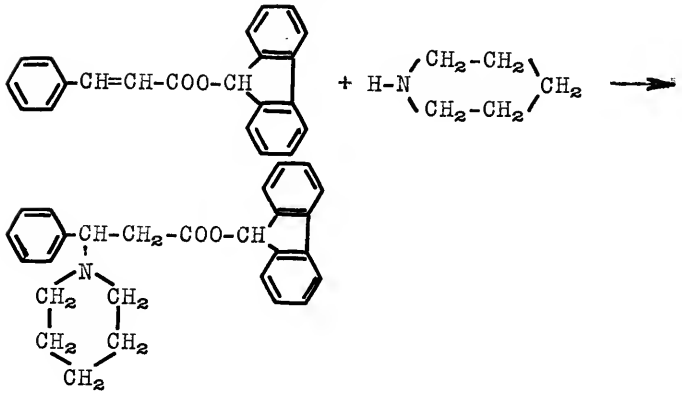
Water. . . . . Soluble

Ethanol. . . . . Soluble

Acetone. . . . . Insoluble

Ether. . . . . Insoluble

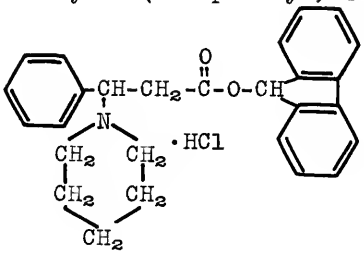
9-Fluorenyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Fifteen and six-tenths grams of 9-fluorenyl cinnamate and 4.25 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized from propanol-2.

Yield: 3.0 g., or 13.8%.

9-Fluorenyl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . $C_{27}H_{28}N\ O_2Cl$

Molecular Weight. 433.96

Melting Point. . . . . 192.5 - 193

Recrystallizing Solvent. Hexane-Propanol-2

Analyses:

Carbon, %

Calculated. . . . 74.72

Found. 74.79

Hydrogen, %

Calculated. 6.50

Found. 6.69

Solubilities:

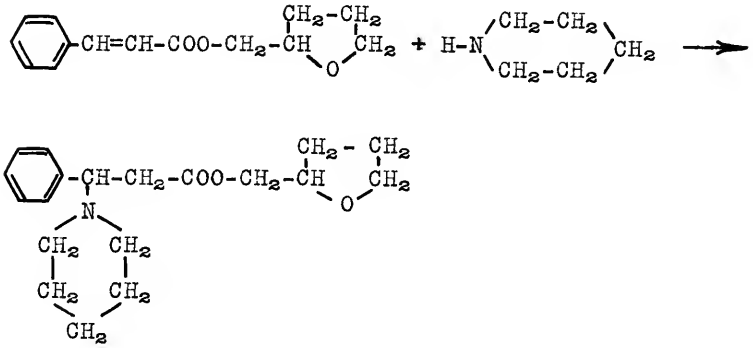
Water. . . . . Soluble

Ethanol. . . . . Soluble

Acetone. . . .Slightly Soluble

Ether. . . . . Insoluble

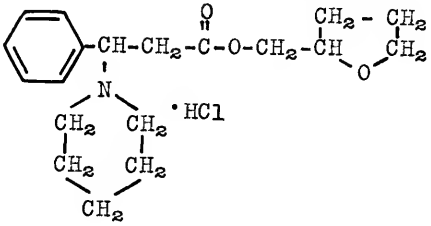
Tetrahydrofurfuryl 2-(1-Piperidyl)-2-phenyl-propionate Hydrochloride



Fifteen grams of tetrahydrofurfuryl cinnamate and 5.5 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was then recrystallized three times from propanol-2.

Yield: 4.8 g., or 13.5%.

Tetrahydrofurfuryl 2-(1-Piperidyl)-2-phenyl-propionate
Hydrochloride



Molecular Formula. . . . . .$C_{19}H_{28}NO_3Cl$

Molecular Weight. 353.88

Melting Point. . . . . 156.7 - 157.5

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 64.46

Found. 64.10

Hydrogen, %

Calculated. 7.98

Found. 8.16

Solubilities:

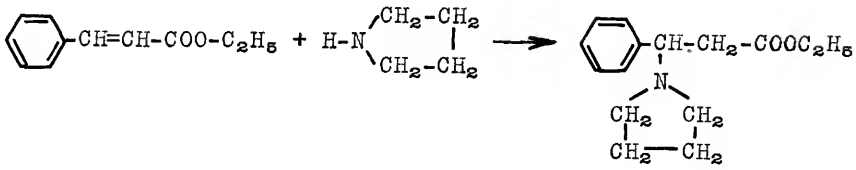
Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Acetone. . . . . Slightly Soluble

Ether. . . . . .Insoluble

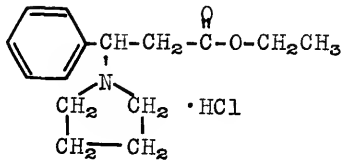
Ethyl 2-(1-Pyrrolidyl)-2-phenyl-propionate Hydrochloride



Thirty-five and two-tenths grams of ethyl cinnamate and 14.2 g. of piperidine were dissolved in 30 ml. of toluene and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 60-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was then extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 10.3 g. or 18.2%.

Ethyl 2-(1-Pyrrolidyl)-2-phenyl-propionate Hydrochloride



Molecular Formula. . . . . .$C_{15}H_{22}N\,O_2Cl$

Molecular Weight. 283.80

Melting Point. . . . . 175.5 - 176

Recrystallizing Solvent. Propanol-2

Analyses:

Carbon, %

Calculated. 63.62

Found. 63.28

Hydrogen, %

Calculated. 7.82

Found. 7.76

Solubilities:

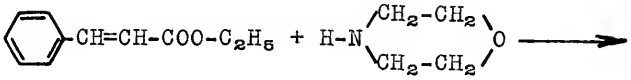
Water. . . . . .Very Soluble

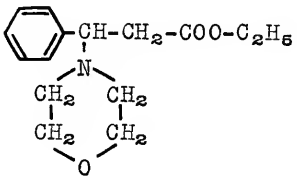
Ethanol. . . . . Soluble

Acetone. . . . . Insoluble

Ether. . . . . Insoluble

Ethyl 2-(4-Morpholinyl)-2-phenyl-propionate Hydrochloride

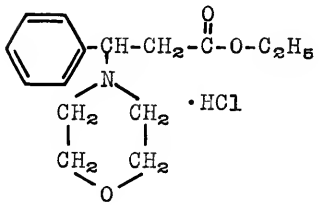




Seventeen and six-tenths grams of ethyl cinnamate and 8.7 g. of morpholine were dissolved in 30 ml. of toluene, and the solution was refluxed for twenty hours. After the solution had been cooled to room temperature it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized three times from propanol-2.

Yield: 6.0 g. or 20%.

Ethyl 2-(4-morpholinyl)-2-phenyl-propionate Hydrochloride



Molecular Formula . . . . . $C_{17}H_{26}NO_2Cl$

Molecular Weight. 299.80

Melting Point 201

Recrystallizing Solvent Propanol-2

Analyses:

Carbon, %

Calculated. 60.09

Found 60.43

Hydrogen, %

Calculated. 7.40

Found 7.49

Solubilities:

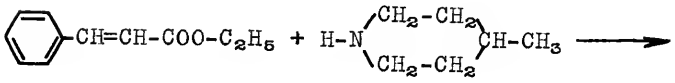
Water. . . . . Very Soluble

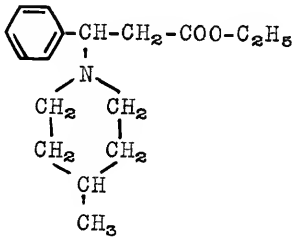
Ethanol. . . . . .Soluble

Acetone. . . . . .Insoluble

Ether. . . . . .Insoluble

Ethyl 2-[1-(4-Methyl)-piperidyl]-2-phenyl-propionate Hydrochloride

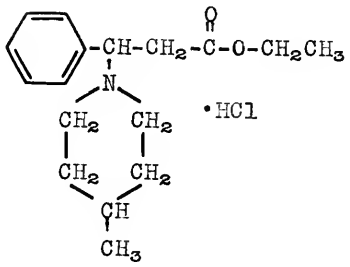




Seventeen and six-tenths grams of ethyl cinnamate and 9.9 g. of piperidine were dissolved in 30 ml. of heptane, and the solution was refluxed for eight hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized from propanol-2.

Yield: 5.3 g., or 17%.

Ethyl 2-[1-(4-Methyl)-piperidyl] -2-phenyl-propionate
Hydrochloride



Molecular Formula . . . . . $C_{17}H_{26}NO_2Cl$

Molecular Weight. 311.85

Melting Point . . . . . 215 - 216

Recrystallizing Solvent Propanol-2

Analyses:

Carbon, %

Calculated. . . 65.47

Found 65.42

Hydrogen, %

Calculated. . . .8.42

Found 8.40

Solubilities:

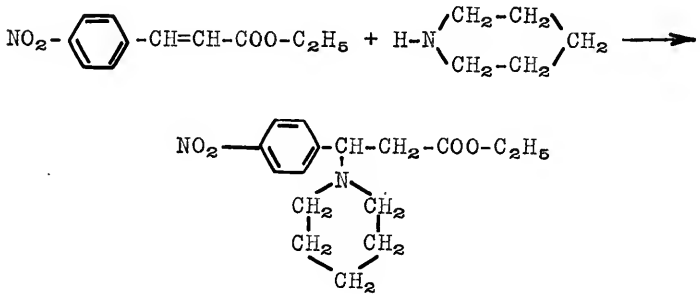
Water. . . . . .Very Soluble

Ethanol. . . . . Soluble

Acetone. . . . . Insoluble

Ether. . . . . Insoluble

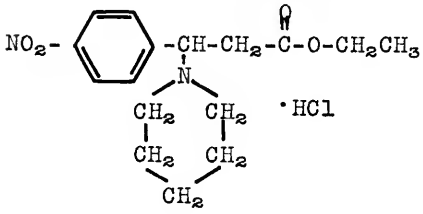
Ethyl 2-(1-Piperidyl)-2-(4-nitrophenyl)-propionate Hydrochloride



Fifteen and six-tenths grams of ethyl 4-nitrocinnamate and 6.0 g. of piperidine were dissolved in 30 ml. of heptane. To this solution was added 1 ml. of a 10% solution of tetramethylammonium hydroxide. The solution was refluxed for eight hours. After the solution had been cooled to room temperature, it was washed with three 30-ml. portions of distilled water. The organic layer was then extracted with two 30-ml. portions of cold 3 N hydrochloric acid. These acid aqueous extracts were combined and made basic to pH 8 by the addition of granular potassium carbonate. The resultant oil was extracted with two 50-ml. portions of ether. The ethereal extracts were combined and dried over anhydrous calcium sulfate. The dry ether solution was treated with hydrogen chloride until acid to Congo Red paper. The precipitated white solid was recrystallized twice from propanol-2.

Yield: 6.6 g., or 27.3%.

Ethyl 2-(1-Piperidyl)-2-(4-nitrophenyl)-propionate
Hydrochloride



Molecular Formula . . . . . $C_{16}H_{23}N_2O_4Cl$

Molecular Weight. 342.82

Melting Point . . . . . 191 - 192

Recrystallizing Solvent Propanol-2

Analyses:

Carbon, %

Calculated 56.06

Found. 55.98

Hydrogen, %

Calculated 6.76

Found. 6.69

Solubilities:

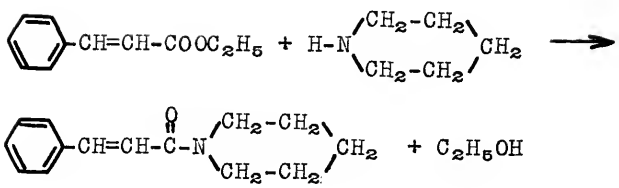
Water. . . . . .Soluble

Ethanol. . . . . .Soluble

Acetone. . . . . .Insoluble

Ether. . . . . .Insoluble

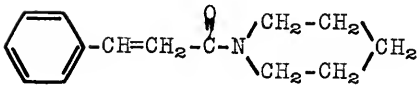
1-Cinnamylpiperidine



A mixture of 52.8 g. of ethyl cinnamate and 25.5 g. of piperidine was refluxed for seventy hours. The unchanged reactants and ethanol were then removed by distillation at 0.50 mm. Hg. When the temperature reached 80° the distillation was discontinued. After cooling to room temperature the material in the pot solidified. This was recrystallized twice from ethanol and washed with petroleum ether.

Yield: 46.5 g., or 71.3%.

1-Cinnamylpiperidine



Molecular Formula . . . . . $C_{14}H_{18}N$ O

Molecular Weight. 215.29

Melting Point . . . . . 118 - 119.5

Recrystallizing Solvent . . . . . Ethanol

Analyses:

Carbon, %

Calculated. 78.14

Found 78.23

Hydrogen, %

Calculated. 7.97

Found 8.03

Solubilities:

Water . . . . . .Insoluble

Ethanol . . . . . .Soluble

Acetone . . . . . .Soluble

Ether . . . . . .Soluble

Part 2: The Preparation of Intermediates

Amines

The piperidine used in this investigation was practical grade material obtained from Matheson, Coleman, and Bell Company. It was redistilled before use. The fraction boiling at 106° was collected.

The morpholine used was obtained from Carbide and Carbon Chemicals Company. It was redistilled before being used. The fraction boiling at 128 to 129° was collected.

The pyrrolidine was purchased from the Brothers Chemical Company. It was redistilled; the fraction boiling at 86 to 87° was collected.

The 2-methylpiperidine, 3-methylpiperidine, and 4-methylpiperidine were formed by reduction of the corresponding methylpyridines. The freshly distilled methylpyridine was reduced under 4000 lbs. pressure of hydrogen at 200° for eight hours, using a Raney nickel catalyst. After the products had been decanted from the catalyst they were distilled at atmospheric pressure. The 2-methylpiperidine boiled at 118-119°; the 3-methylpiperidine at 125-126°; the 4-methylpiperidine at 125-126°.

The 2-amylpiperidine was obtained by the reduction of 2-amylpyridine. The 2-amylpyridine was prepared by the reaction of 2-methylpyridine and n-butyl chloride with sodamide according to the method of Vaughn et al.[17] The 2-amylpyridine boiled at 117-120° at 40 mm. Hg. It was reduced at 200° under a pressure of 2000 lbs. of hydrogen, using a Raney nickel catalyst. The 2-amylpiperidine was distilled at 40 mm. Hg.; it boiled at 115.5 to 117°. The overall yield was 63.5%.

The di(n-butyl)amine was obtained from the Hooker Electrochemical Company and was used without further purification.

Cinnamate Esters

The ethyl cinnamate was obtained from Brothers Chemical Company. It was redistilled before using. The fraction boiling at 128-130° at 6.0 mm. Hg. was collected.

The beta-substituted cinnamate esters were prepared by the Reformatsky reaction according to the method described in "Organic Reactions," Volume I.[18] Ethyl 2-ethylcinnamate boiled at 106-108° at 1.5 mm. Hg. Ethyl 2-phenylcinnamate boiled at 153-157° at 2.0 mm. Hg.

Ethyl p-nitrocinnamate was prepared by the nitration and esterification of cinnamic acid.[19] The melting point of this compound was 137-138°.

The unsubstituted cinnamate esters, other than the ethyl ester, were prepared by reacting cinnamyl chloride with the corresponding alcohol in the presence of pyridine. The cinnamyl chloride was formed by refluxing a benzene solution of cinnamic acid and thionyl chloride for eight hours. The solvent was then removed on the steam bath under water pump vacuum. The cinnamyl chloride was then used without further purification.

All of the unsubstituted cinnamate esters were synthesized according to the same procedure. Two-tenths of a mole of cinnamyl chloride was added portionwise, with ice bath cooling, to a solution of 0.2 moles of the alcohol and 0.2 moles of pyridine in 100 ml. of benzene. The reaction mixture was allowed to stand at room temperature for twenty-four hours. It was then extracted with three 50 ml. portions of distilled water. The organic layer was separated and dried over anhydrous calcium sulfate. The solvent was then removed by distillation on the steam bath under water-pump vacuum. The residue was vacuum distilled. The yields and physical constants of the products are listed in Table 1.

TABLE 1

CINNAMATE ESTERS

Ester	Boiling Point °C.	Boiling Point mm. Hg.	Refractive Index	% Yield	Reference
Methyl	36 (a)		----	75.4	20
n-Propyl	92-94	0.50	1.5474	79.0	20
n-Butyl	98-100	0.50	1.5410	73.4	21
sec-Butyl	87-89	0.35	1.5380	78.8	(b)
iso-Butyl	90-92	0.25	1.5377	85.9	22
n-Amyl	104-106	0.50	1.5378	74.2	(b)
sec-Amyl	102-104	0.50	1.5369	84.5	(b)
n-Hexyl	114-115	0.45	1.5591	63.8	(b)
Benzyl	39 (a)		----	50.3	23
1-Phenylethyl	156-159	0.60	1.5957	65.8	(b)

TABLE 1 (Continued)

Ester	Boiling Point °C.	Boiling Point mm. Hg.	Refractive Index	% Yield	Reference
9-Fluorenyl	76.5-77.5 (a)		-----	74.8	(b)
p-Bromobenzhydryl	87-88 (a)		-----	58.7	(b)
Cyclohexyl	114-116	0.200	1.5591	87.0	21
2-Methoxy-1-methylethyl	118-120	1.00	1.5417	62.3	(b)
Tetrahydrofurfuryl	129-131	0.650	1.5632	35.4	24
2-(2-Methoxy)-ethoxyethyl	134-136	0.650	1.5633	45.9	(b)

(a) indicates melting point

(b) compound not reported in the literature

Part 3: A Study of the Reaction of Heterocyclic Amines with Cinnamate Esters

The experimental work described in this section was undertaken to study various means of increasing yields of 2-(N-heterocyclic)-2-phenyl-propionate esters, and to investigate the nature of the reaction of a heterocyclic amine with a cinnamate ester.

The effects of various solvents, catalytic substances, molar proportions of reactants, and reaction times upon the yield were determined. In all of the work on this phase of the problem ethyl cinnamate and piperidine were used as the reactants. Unless otherwise noted, all yields reported in this section refer to crude, unrecrystallized product.

There are very few reports in the literature to the reaction of amines with cinnamate esters. Some of the work described here tends to clarify the chemistry of the reaction. Data is presented which indicates the reversible nature of the reaction. Secondary amines and cinnamate esters which did not react are discussed because they tend to define the scope and limitations of the reaction.

Percent Conversion

A solution of 17.6 g. (0.1 mole) of ethyl cinnamate, 8.5 g. (0.1 mole) of piperidine and 1 ml. of a 10% solution of tetramethylammonium hydroxide in 30 ml. of toluene was refluxed for twenty hours. After the solution had been cooled, it was washed with three 30-ml. portions of distilled water. The solution was then extracted with two 30-ml. portions of 3 N hydrochloric acid. The organic layer was separated, dried over anhydrous calcium sulfate and distilled under vacuum. Eight and nine-tenths grams of ethyl cinnamate (n^{25} 1.5593) boiling at 78-79° at 1.10 mm. Hg were recovered. The aqueous acid extract was cooled, made basic with granular potassium carbonate and extracted with ether. The dry ethereal solution was treated with dry hydrogen chloride, yielding 14.2 g. of ethyl 2-(1-piperidyl)-2-phenyl-propionate hydrochloride.

Moles of ester used:	0.100
Moles of ester recovered:	0.051
Moles of ester reacted:	0.049
Moles of product isolated:	0.048
Percentage Yield:	48%
Percentage Conversion:	98%

The Effect of Various Solvents Upon Yield

Ethyl cinnamate and piperidine were refluxed in various solvents for twenty hours. No catalysts were used. The product was isolated as described on the preceding page.

Solvent	Percentage Yield
Toluene	26.5
Heptane	20.1
n-Butanol	20.8
None	23.4

The Effect of Catalysts Upon Yield

Two series of tests were run, one using heptane as a solvent, the other using toluene. In each case the substance was employed in the form of a 10% aqueous solution. One milliliter of the solution containing the catalyst was added to a solution of 0.1 mole of each reactant in 30 ml. of solvent.

Heptane, refluxed 8 hours:

Catalyst	Percentage Yield
Tetramethylammonium Hydroxide	32.9
Tetramethylammonium Bromide	11.1
Sodium Hydroxide	8.7
None	8.5

Toluene, refluxed 20 hours:

Catalyst	Percentage Yield
Tetramethylammonium Hydroxide	47.7
Water	26.9
None	26.5

The Effect of Reaction Time Upon Yield

Two series of tests were made, one using heptane as the solvent, the other using toluene. In both cases equimolar quantities of reactants were employed. The product was isolated in the manner described on page 56.

The first test was run on a heptane solution of the reactants, containing no catalyst. The temperature was the reflux temperature of the solution.

Time in Hours	Percentage Yield
3	3.9
7	7.2
10	8.3
14	10.3
22	14.7
31	16.5
50.5	20.5
58	22.8
75	25.8

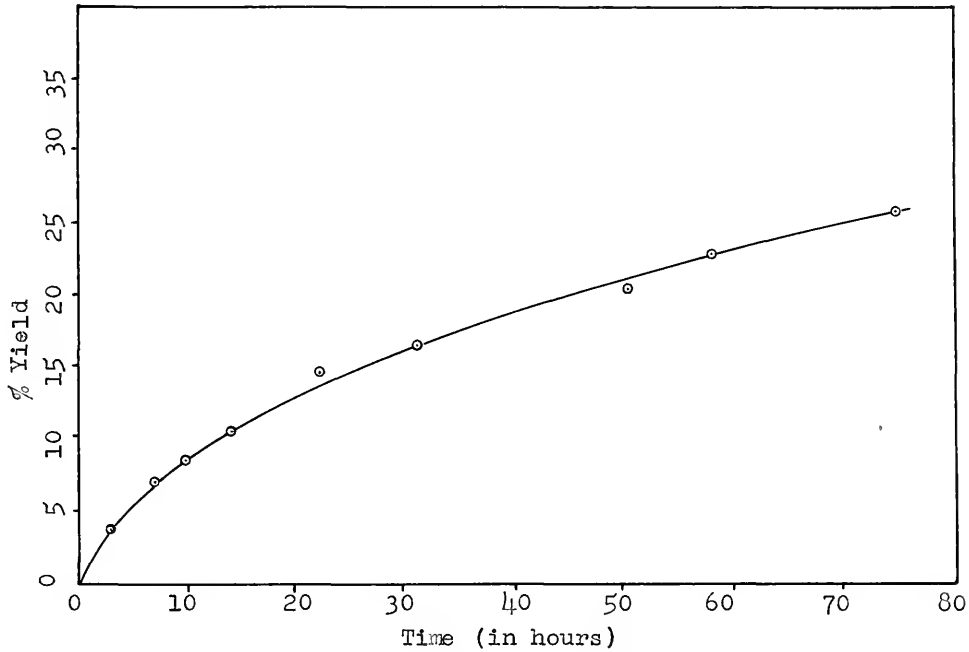


Fig. 1.--Relationship between reaction time and yield of product. Heptane solution, no catalyst.

The second test was run on a toluene solution of the reactants, containing 5 ml. of a 10% solution of tetramethylammonium hydroxide. The temperature was the reflux temperature of the solution.

Time in Hours	Percentage Yield
5	20.3
10	36.0
15	40.5
20	45.1
25	43.2

The relationship of yield to reaction time for these two runs is expressed graphically in Figures 1 and 2.

The Effect of Employing Excess Piperidine Upon Yield

These tests were run in toluene solution, with no catalyst. The solutions were refluxed for twenty hours.

Moles of Piperidine per Mole of Ethyl Cinnamate	Percentage Yield	
	Crude	Recrystallized
1	26.5	16.7
3	75.2	47.3

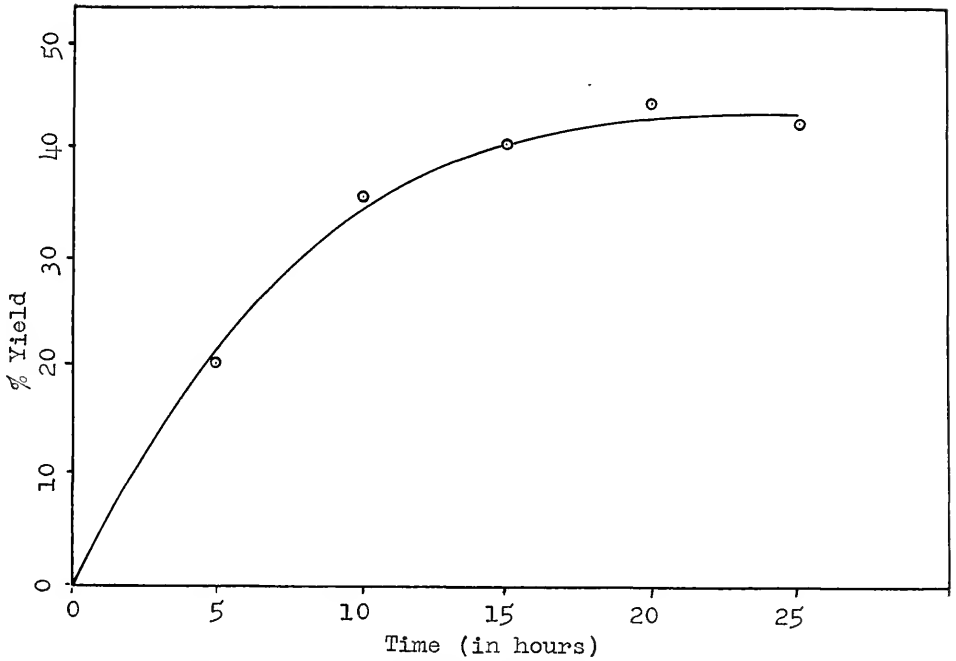


Fig. 2.--Relationship between reaction time and yield of product. Toluene solution, tetramethylammonium hydroxide catalyst.

Negative Reactions

The pairs of substances listed below did not react when refluxed eight to twenty hours in heptane or toluene solution. The unchanged amine was isolated in each case.

(a) ethyl 2-phenylcinnamate and piperidine
(b) ethyl 2-phenylcinnamate and pyrrolidine
(c) ethyl 2-phenylcinnamate and 4-methylpiperidine
(d) ethyl 2-phenylcinnamate and morpholine
(e) ethyl 2-phenylcinnamate and 2-methylpiperidine
(f) ethyl 2-phenylcinnamate and 2-amylpiperidine
(g) ethyl 2-ethylcinnamate and piperidine
(h) ethyl 2-ethylcinnamate and pyrrolidine
(i) ethyl 2-ethylcinnamate and morpholine
(j) ethyl 2-ethylcinnamate and 4-methylpiperidine
(k) ethyl 2-ethylcinnamate and 2-methylpiperidine
(l) ethyl 2-ethylcinnamate and 2-amylpiperidine
(m) ethyl cinnamate and 2-methylpiperidine
(n) ethyl cinnamate and 2-amylpiperidine
(o) ethyl cinnamate and 1-phenylpiperazine
(p) ethyl cinnamate and di(n-butyl)amine

The expected beta-amino ester was not isolated when the pairs of substances listed below were refluxed in toluene solution for twenty hours. The unchanged olefinic ester was recovered in each case.

(a) 2-(diethylamino)ethyl cinnamate and piperidine

(b) 2-(dimethylamino)ethyl cinnamate and piperidine

(c) 3-(diethylamino)propyl cinnamate and piperidine

(d) 2-(2-methoxyethoxy)-ethyl cinnamate and piperidine

The following pairs of substances, when reacted, yielded only viscous oils which could not be crystallized.

(a) ethyl cinnamate and 3-methylpiperidine

(b) ethyl cinnamate and 4-ethylpiperidine .

(c) p-methoxybenzyl cinnamate and piperidine

(d) benzhydryl cinnamate and piperidine

(e) p-methylbenzhydryl cinnamate and piperidine

(f) 1-phenylpropyl cinnamate and piperidine

Ethyl 2-phenylcinnamate and ethyl 2-ethylcinnamate did not react with any of the heterocyclic amines. It is probable that this is due to resonance and steric effects. Because two phenyl groups are conjugated with the olefinic bond in the 2-phenylcinnamate ester six nonreacting, competing resonance forms are possible. Similarly in the case of the 2-ethylcinnamate ester steric hindrance and resonance effects due to hyperconjugation would tend to decrease the reactivity of the ester.

Piperidines which are substituted in the alpha-position do not react with cinnamate esters. Since the

electronic effects of such substitutions should tend to increase the reactivity of the amine, the lack of reaction must be due to steric causes.

The failure of 1-phenylpiperazine to react with ethyl cinnamate is not surprising. Pollard and Robbins found that 1-arylpiperazines did not react with 2-methylacrylate esters,[25] which could be expected to be more reactive than the cinnamate esters.

The only aliphatic secondary amine used, di(n-butyl)-amine, did not react. It has been stated that aliphatic secondary amines in general give lower yields than the heterocyclic amines when reacted with acrylate esters.[8] It may be that this general trend applies to the reaction of amines with cinnamate esters.

The failure to isolate any product from the reaction of the dialkylaminoalkyl cinnamate esters with piperidine may be due to the method of working up the reaction mixture rather than a lack of reactivity of the ester. Because the product could not be separated from the cinnamate ester by extraction with an acid solution, isolation was attempted by vacuum distillation. Piperidine has the lowest boiling point of any of the substances in the equilibria which is probably involved. This could have shifted the equilibrium in the direction of the reactants during the distillation.

In summary, a few generalizations can be made: (1) Cinnamate esters which are substituted in the beta-position with an alkyl or aryl group do not react with heterocyclic amines. (2) Heterocyclic amines which are substituted in the alpha-position do not react with cinnamate esters.

Stability of Products

In all cases the 2-(N-heterocyclic)-2-phenyl-propionate esters were stable in the form of their hydrochloride salts. There was no evidence of decomposition in aqueous solution or in boiling propanol-2. Pollard and Stewart[26] report that 4-chalcone morpholine is unstable in the form of its hydrochloride salt.

Attempts to form quarternary salts of ethyl 2-(1-piperidyl)-2-phenyl-propionate resulted in decomposition. When methyl iodide was reacted with this compound at room temperature N,N-dimethylpiperidinium iodide was formed. This substance was identified by melting point and mixed melting point with an authentic sample.

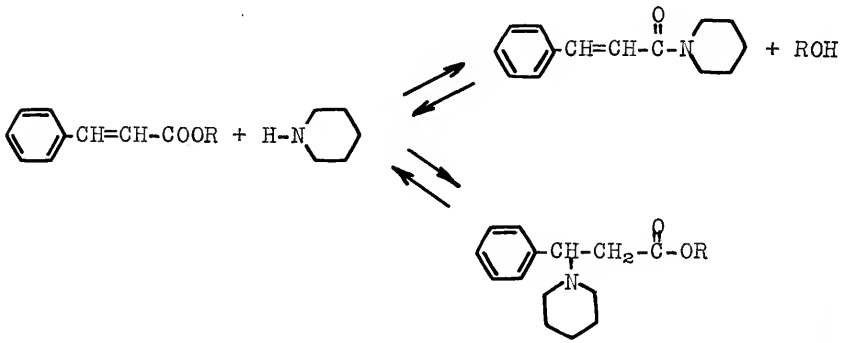
Evidence of the Reversibility of the Reaction

An equimolar mixture of ethyl cinnamate and piperidine was refluxed without a solvent. Periodically the refractive index of this mixture was measured.

A sample of ethyl 2-(1-piperidyl)-2-phenyl-propionate was refluxed without a solvent. The refractive index was measured periodically.

A plot of refractive indices against time (Figure 3) indicates that the two curves approach each other. That the situation is more complex than a simple equilibrium can be seen by the fact that the curves do not become constant at a refractive index between that of the two starting materials. The sharp upward break of the two curves could be considered as an indication of formation of a third substance, 1-cinnamylpiperidine. This substance was isolated from both reaction mixtures. Identification was made by melting point and mixed melting point with an authentic sample of N-cinnamylpiperidine.

This evidence would apparently indicate that the reaction of heterocyclic amines with cinnamate esters involves the following equilibria:



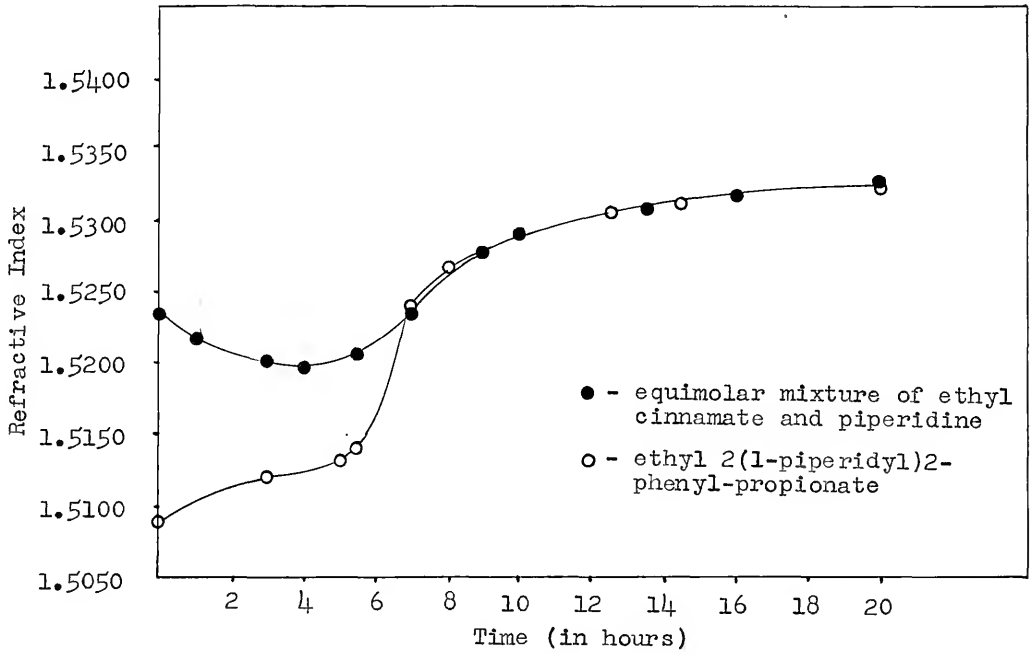

1.5400
1.5350
1.5300
1.5250
1.5200
1.5150
1.5100
1.5050
Refractive Index
2
4
6
8
10
12
14
16
18
20
Time (in hours)
● - equimolar mixture of ethyl cinnamate and piperidine
o - ethyl 2(1-piperidyl)2-phenyl-propionate

Fig. 3

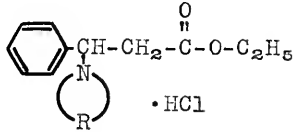
CHAPTER IV

SUMMARY

The addition of heterocyclic amines to cinnamate esters has been shown to be a practical method of synthesizing 2-(N-heterocyclic)-2-phenyl-propionate esters. The effects of various conditions upon the yield have been studied. Evidence has been obtained which indicates the nature of the equilibria involved in this reaction. The preparation of nineteen new 2-(N-heterocyclic)-2-phenyl-propionate esters has been described in detail. The properties of these compounds are summarized in Tables 2, 3, and 4.

TABLE 2

ETHYL 2-(N-HETEROCYCLIC)-2-PHENYL-PROPIONATE HYDROCHLORIDES



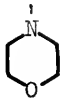
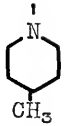
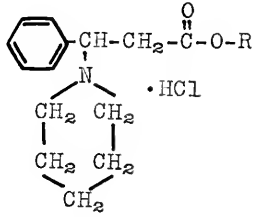
Heterocyclic Group		Molecular Weight	Emperical Formula	Yield	Carbon, %		Hydrogen, %	
					Calc.	Found	Calc.	Found
1-Pyrollidyl		283.80	$C_{15}H_{22}NO_2Cl$	18.2	63.62	63.28	7.82	7.76
1-Piperidyl		297.81	$C_{16}H_{24}NO_2Cl$	20.1	64.52	64.36	8.12	8.22
4-Morpholinyl		299.80	$C_{15}H_{22}NO_3Cl$	20.0	60.09	60.43	7.40	7.49
1-(4-Methyl)-piperidine		311.85	$C_{17}H_{26}NO_2Cl$	17.0	65.47	65.42	8.42	8.40

TABLE 3

ALKYL 2-(1-PIPERIDYL)-2-PHENYL-PROPIONATE HYDROCHLORIDES



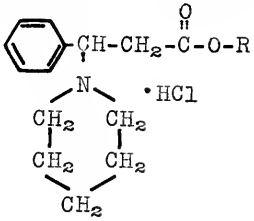
Alkyl Group	R	Molecular Weight	Molecular Formula	Yield	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found
Methyl	$-CH_3$	283.80	$C_{15}H_{22}NO_2Cl$	18.6	63.47	63.34	7.82	7.95
Ethyl	$-CH_2-CH_3$	297.82	$C_{16}H_{24}NO_2Cl$	20.1	64.52	64.36	8.12	8.22
n-Propyl	$-CH_2-CH_2-CH_3$	311.85	$C_{17}H_{26}NO_2Cl$	22.4	65.47	65.83	8.42	8.55
n-Butyl	$-(CH_2)_3-CH_3$	325.87	$C_{18}H_{28}NO_2Cl$	15.6	66.33	66.10	8.67	8.68
n-Amyl	$-(CH_2)_4-CH_3$	399.90	$C_{19}H_{30}NO_2Cl$	12.2	67.13	67.24	8.91	8.76
n-Hexyl	$-(CH_2)_5-CH_3$	353.93	$C_{20}H_{32}NO_2Cl$	7.9	67.86	67.76	9.13	9.22

TABLE 3 (Continued)

Alkyl Group	R	Molecular Weight	Molecular Formula	Yield	Carbon, %		Hydrogen, %	
					Calc.	Found	Calc.	Found
2-Methylpropyl	$-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-CH_3$	325.87	$C_{18}H_{28}NO_2Cl$	6.5	66.33	66.16	8.67	8.55
1-Methylpropyl	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-CH_2-CH_3$	325.87	$C_{18}H_{28}NO_2Cl$	6.3	66.33	66.48	8.67	8.57
1-Methylbutyl	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-CH_2-CH_2-CH_3$	339.90	$C_{19}H_{30}NO_2Cl$	3.7	67.13	67.10	8.91	8.87

TABLE 4

ESTERS OF 2-(1-PIPERIDYL)-2-PHENYL-PROPIONIC ACID HYDROCHLORIDE



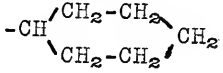
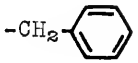
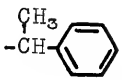
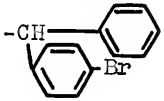
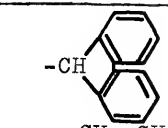
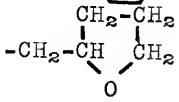
Ester	R	Molecular Weight	Molecular Formula	Yield	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found
Cyclohexyl		351.91	$C_{20}H_{30}NO_2Cl$	9.9	68.26	68.00	8.59	8.45
Benzyl		359.88	$C_{20}H_{26}NO_2Cl$	20.3	70.08	69.72	7.28	7.32
1-Phenyl-ethyl		373.91	$C_{22}H_{28}NO_2Cl$	13.5	70.66	70.65	7.55	7.65
p-Bromobenz-hydryl		514.89	$C_{27}H_{28}NO_2ClBr$	24.4	62.97	63.23	5.68	5.60

TABLE 4 (Continued)

Ester	R	Molecular Weight	Molecular Formula	Yield	Carbon, %		Hydrogen, %	
					Calc.	Found	Calc.	Found
9-Fluorenyl		433.96	$C_{27}H_{28}NO_2Cl$	13.8	74.72	74.79	6.50	6.69
Tetrahydro-furfuryl		353.88	$C_{18}H_{28}NO_3Cl$	13.5	64.47	64.10	7.98	8.16

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Mr. Mattson received the Degree of Bachelor of Science at Union College, Schenectady, New York, in June, 1949. He attended Columbia University on a part-time basis from September, 1949, to June, 1950. He was enrolled as a part-time student in the Graduate School of The Polytechnical Institute of Brooklyn, from September, 1950, to June, 1951. He entered the University of Florida in June, 1952.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of the committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1955

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